(12)

AAMRL-TR-87-045

NMRI-87-40

TOXIC EFFECTS OF MAN-MADE MINERAL FIBERS WITH PARTICULAR REFERENCE TO CERAMIC FIBERS

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SEPTEMBER 1987

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

Melvin E Andersen

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AD-A187949

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S) AAMRL-TR-87-045, NMRI 87-40
6a. NAME OF PERFORMING ORGANIZATION Northrop Services, Incorporated 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION AAMRL, Toxic Hazards Division
6c. ADDRESS (City, State, and ZIP Code) 101 Woodman Drive, Suite 12 Dayton, Ohio 45431	7b. ADDRESS (City, State, and ZIP Code) HSD, AFSC Wright-Patterson AFB, Ohio 45433-6573
8a. NAME OF FUNDING/SPONSORING ORGANIZATION 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER F33615-85-C-0532
8c. ADDRESS (City, State, and ZIP Code)	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 62202F; PROJECT NO. 6302; TASK NO. 00; WORK UNIT ACCESSION NO. 01

11. TITLE (Include Security Classification)
Toxic Effects of Man-Made Mineral Fibers with Particular Reference to Ceramic Fibers

12. PERSONAL AUTHOR(S)
Dr Allen Vinegar

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Technical Report	FROM 12/86 TO 01/87	September 1987	33

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Adenoma, Carcinoma, Ceramic Fibers, Chrysotile, Cristobalite, Crocidolite, Durability, Fibrosis, Fibrous Glass, Glass Wool, Inhalation, Intraperitoneal Injection, Intrapleural Injection (See Reverse)
06	20		
11	05		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

In order to evaluate the potential hazards of man-made mineral fibers (MMMF); particularly ceramic fibers, in the Navy work environment, the following areas are considered. First, the current standards and recommendations of other agencies are presented as an overview of current concensus as to relative hazards of asbestos, MMMF, and cristobalite (a form of crystalline silica). Then, a summary of recent epidemiological evidence is presented. These data should be the most relevant for human exposure. Unfortunately, there are no data for workers in the ceramic fiber field. Then a review is presented of the data from animal experiments which employed exposure by inhalation, intratracheal instillation, and intrapleural or intraperitoneal injection. The experiments reviewed involve only non-ceramic MMMF. Some detail of the protocol and results of each experiment are presented to provide a better understanding of the non-uniformity of the protocols used. Another issue of particular importance in understanding fiber toxicity is the durability of the fiber. These data are presented for non-ceramic MMMF. Then, the scant literature on ceramic fibers is addressed, followed by a discussion of all the above-mentioned information as it relates to the toxicity and hazard posed by ceramic-fiber exposure. Based on evaluation of the above-mentioned evidence, recommendations for future research is made.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION
22a. NAME OF RESPONSIBLE INDIVIDUAL Melvin E. Andersen, Ph.D.	22b. TELEPHONE (Include Area Code) (513) 255-3916 22c. OFFICE SYMBOL AAMRL/TH

DD Form 1473, JUN 86 Previous editions are obsolete. SECURITY CLASSIFICATION OF THIS PAGE

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18. **Intratracheal Instillation, Leukemia, Man-Made Mineral Fibers, Mesothelioma, Mineral Wool, Rock Wool, Sarcoma, Slag Wool.**

PREFACE

This document presents information on the toxic effects of man-made mineral fibers and, in particular, ceramic fibers, for use by the U.S. Navy in assessing the risk of exposure to these substances in the Navy work environment. This information was gathered and assessed by Northrop Services, Incorporated - Environmental Sciences which operates the Toxic Hazards Research Unit of the Toxic Hazards Division, Harry G. Armstrong Aerospace Medical Research Laboratory at Wright-Patterson AFB under Contract Number F33615-85-C-0532. Dr. Melvin E. Andersen is presently the Contract Technical Monitor for the U.S. Air Force.

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The work was sponsored by the U.S. Navy under the direction of CAPT D. E. Uddin, MSC, USN. The study is identified as Work Unit Number MF-58524001.0006.

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DEFINITIONS

ACGIH	American Conference of Governmental Industrial Hygienists
BAH	bronchoalveolar hyperplasia
CD	cesarean delivered
CMD	count median diameter
CML	count median length
f/cc	fibers per cubic centimeter
f/L	fibers per liter
f/m^3	fibers per cubic meter
GSH	goblet cell hyperplasia
IARC	International Agency for Research on Cancer
IP	intraperitoneal
IT	intratracheal
LHD	Landing Ship, Helicopter Dock
MMMF	man-made mineral fibers
mppcf	million particles per cubic foot
NIOSH	National Institute for Occupational Safety and Health
OM	Osborne-Mendel
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit (OSHA)
refractory	heat-resistant
REL	recommended exposure limit (NIOSH)
SPF	specific pathogen free
TLV	threshold limit value
TWA	time-weighted average
UICC	Union Internationale Contre le Cancer
WHO	World Health Organization

The following figure adapted from Omenn *et al.* (1986) shows the relationship between the fiber types considered in this report.

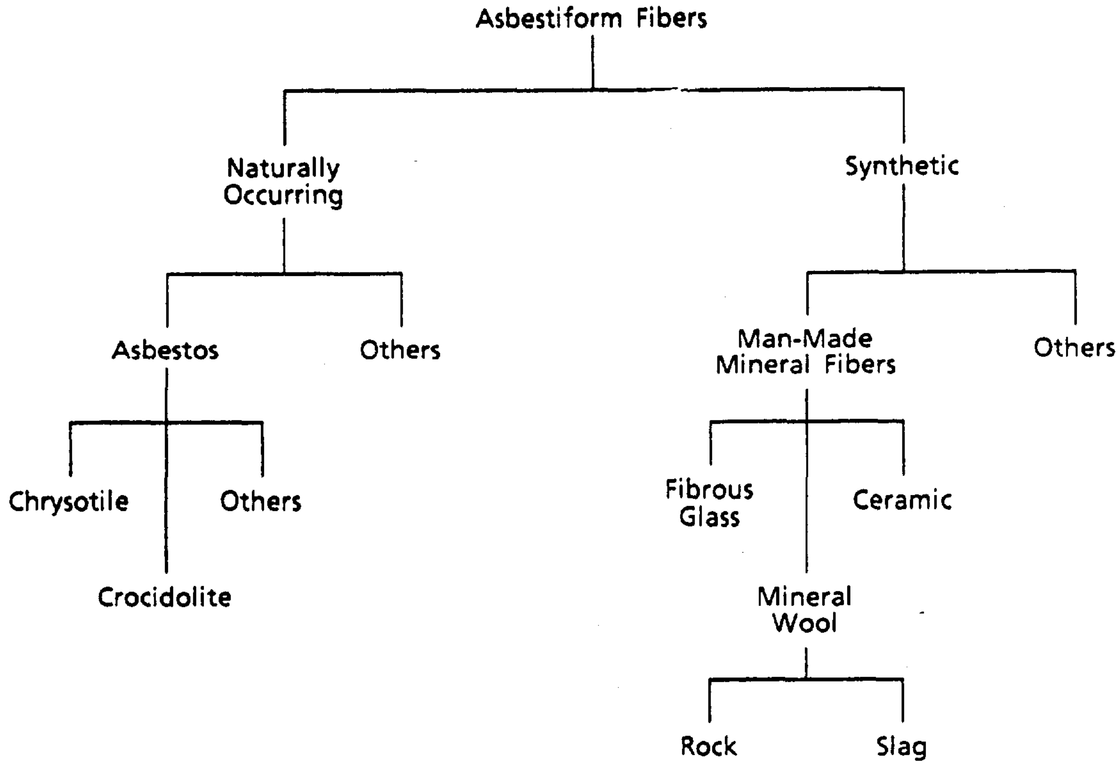

Figure 1. This chart adapted from Omenn *et al.* (1986) shows the relationship between the fiber types considered in this report.

SECTION 1

BACKGROUND

In recent years both ceramic fiber and mineral wool have been used to replace asbestos on board many U.S. Navy ships. In particular, material manufactured from refractory ceramic fiber is being used in the boilers of Landing Ship, Helicopter Dock (LHD) class ships. There has been recent indication that ceramic fibers may present a greater health hazard than other man-made mineral fibers (MMMF). In view of this problem, the Navy must determine the toxic properties of the various MMMF and establish a Navy-wide standard for such fibers. The lack of an easily applied field method that differentiates between bulk and airborne fibers complicates matters. The only accepted, easily applied method for calculating fiber counts from air samples is the physical and chemical analytical method (P&CAM) 7400 for asbestos which is used by the National Institute for Occupational Safety

and Health (NIOSH). However, this nonspecific method does not differentiate between fiber types. Since it is not possible to analytically distinguish between fibers, a 2f/cc standard was adopted until further information is available.

To evaluate the potential hazards of MMMF (particularly ceramic fibers) in the Navy work environment, the following topics in this report will be considered. (1) Current standards and recommendations of various other agencies will be presented in an overview of the relative hazards of asbestos, MMMF, and cristobalite (a form of crystalline silica). (2) Recent epidemiological evidence will be summarized and presented. These data should be the most relevant for human exposure. Unfortunately, there are no data for workers in the ceramic fiber field. (3) Data from experiments exposing animals by inhalation, intratracheal instillation, and intrapleural or intraperitoneal injection will be reviewed. Only nonceramic MMMF were used in these experiments. Some detail of the protocol and results of each experiment will be included to show how these protocols vary. (4) Data will be presented regarding the durability of nonceramic MMMF. (5) The available literature on ceramic fibers will be presented, followed by a discussion of all the above-mentioned information as it relates to toxicity and hazard of ceramic-fiber exposure. After evaluating this evidence, recommendations for future research will be made.

SECTION 2

CURRENT STANDARDS AND RECOMMENDATIONS

To give some perspective on how the maximum levels of exposure were set to protect human health in the workplace, current recommendations and standards for asbestos, fibrous glass dust, and cristobalite are presented below. Recommendations are presented from the American Conference of Governmental Industrial Hygienists (ACGIH); the National Institute for Occupational Safety and Health (NIOSH); and the Occupational Safety and Health Administration (OSHA). Recommended exposure limits (REL) and permissible exposure limits (PEL) are given as threshold limit values (TLV) and time-weighted averages (TWA). The NIOSH and OSHA information is taken from Morbidity and Mortality Weekly Reports (NIOSH, 1986).

Asbestos

ACGIH (1986) makes the following TLV-TWA recommendations.

Amosite - 0.5 f/cc
Chrysotile - 2 f/cc
Crocidolite - 0.2 f/cc
Other forms - 2 f/cc

The fibers are defined as particles longer than 5 µm, with an aspect ratio equal to or greater than 3:1.

NIOSH's REL is 100,000 f/m^3, over 5 µm in length, with 8-h TWAs for all types of asbestos.

OSHA's PEL is 200,000 f/m^3, over 5 µm in length, with 8-h TWAs for all types of asbestos.

Fibrous Glass

ACGIH recommends a TLV-TWA of 10 mg/m^3, which is equal to the general nuisance dust limit.

NIOSH's REL is 3 million f/m^3 TWA (fibers ≤ 3.5 µm diameter and ≥ 10 µm length; 5 mg/m^3 TWA (total fibrous glass). NIOSH also recommends that this REL apply to other synthetic fibers as well.

OSHA considers fibrous glass a nuisance dust and recommends a PEL of 15 mg/m^3 total dust, with a 5 mg/m^3 respirable fraction.

Crystalline Silica (Cristobalite)

ACGIH recommends a TLV-TWA of 0.05 mg/m^3 respirable cristobalite dust.

NIOSH's REL for crystalline silica (all forms) is 50 $\mu g/m^3$ TWA, respirable free silica.

OSHA's PEL for crystalline silica is $250/\%SiO_2 + 5$ in mppcf, or $10\ mg/m^3/\%SiO_2 + 2$ (respirable quartz).

SECTION 3

EPIDEMIOLOGICAL EVIDENCE

Ideally, the health effects from exposure to MMMF should be determined from actual human data. In the case of cancer, which requires many years to develop, data should be obtained on workers who have been exposed to the suspected fibers over much of their lifetimes. Compared to the asbestos industry, the MMMF industry is young, and early reports on the health effects of these MMMF fibers were based on small numbers of workers exposed for short periods of time. Since an MMMF-related cancer death rate cannot be determined from such a small worker population and short exposure times, only the results of the most recent studies will be considered relevant. Late in

1986, a series of papers was published presenting data on a large, international cohort study that addressed the mortality and cancer incidence of MMMF production workers from 13 factories in 7 western European countries. This study, involving 21,967 workers, was coordinated with the International Agency for Research on Cancer (IARC) (Saracci, 1986; Davis, 1986; Cherrie *et al.*, 1986; Cherrie and Dodgson, 1986; Simonato *et al.*, 1986; Olsen et al., 1986; Claude and Frentzel-Beyme, 1986; Teppo and Kojonen, 1986; Bertazzi *et al.*, 1986; Andersen and Langmark, 1986; Westerholm and Bolander, 1986; Gardner *et al.*, 1986). It was concluded that no adverse long-term health effects (measured as mortality) were recorded throughout almost all areas of the MMMF production industry. It was also concluded that earlier working conditions in the slag wool/rock wool industries (with higher exposure levels than those that exist at present) were responsible for observed lung cancers. It should be noted that all the factories included in the study produced glass fiber and mineral wool (rock/slag), not ceramic fibers.

At the 1986 WHO/IARC conference on MMMF, Sir Richard Doll summarized the findings of the European and American epidemiological studies and reached the following conclusions.

> *There has been a relatively small risk of lung cancer in people employed in the early days of both rock and glass wool sectors of industry amounting to some 50% above normal thirty years after first employment. The added risk, however, is numerically substantial because lung cancer is so common. No risk has been demonstrated in the glass filament sector. The risk has been greater in the rock wool sector than in the glass wool sector. A variety of carcinogens have contributed to the hazard. And I say "have" rather than "may" because some of them are genotoxic and, I believe, must be presumed to cause risks proportional to dose, down to very small amounts. The uncertainty about both the fiber counts in the early days of the industry and the extent of the constitution of other carcinogens makes it impossible to provide a precise quantitative estimate of the likely effects of current levels of exposure. No specific hazard other than the hazard of lung cancer has been established. Taking into account also the results of animal experiments, the experience of the asbestos industry and of the glass filament sector of the MMMF industry and accepting that MMMF fibers are not more carcinogenic than asbestos fibers, we can conclude that exposure to fiber levels of the order of 0.2 respirable fibers per milliliter is unlikely to produce a measurable risk even after another twenty years have passed.*

SECTION 4

NONCERAMIC MAN-MADE MINERAL FIBERS

A summary of animal studies to evaluate the toxicity of various MMMF will follow. Ceramic fibers will be considered in a separate section. Inhalation studies will be emphasized here, because these represent the most direct route of exposure for man. The data will focus on recent studies which are, however, representative of more historical data. However, the protocols and results of these studies vary considerably due to the information available to the investigators at the time. To

provide an overview of the differences in pathology, the relevant papers are presented below in outline form.

Inhalation Studies

Authors:	**Gross *et al.*, 1970**
Animals:	Rats and hamsters of unspecified strains (30/group)
Exposure:	Glass fiber (uncoated, coated with phenol-formaldehyde resin or starch binder) 100 mg/m^3, average diameter – 0.5 µm, average length – 10.0 µm 6 h/day, 5 days/week for 24 months Killed at 6, 12, and 24 months
Results:	Minor tissue reaction, small macrophage accumulation

Authors:	**Lee *et al.*, 1979**
Animals:	Charles River CD Sprague-Dawley rats, male; albino guinea pigs, male; Syrian hamsters, male Numbers per group unspecified for all species
Exposure:	Glass fiber 0.42 mg/L (0.73 x 10^6 f/L >5 µm, average diameter 1.2 µm) 6 hr/day, 5 days/week for 90 days Killed at periods up to 2 years after exposure
Results:	Macrophage reaction with alveolar proteinosis observed at 90 days, resolved by 1 year postexposure; ferruginous bodies present in lungs of guinea pigs and hamsters

Authors:	**Johnson and Wagner, 1980**
Animals:	Specific pathogen free (SPF) Fischer rats (2/group)
Exposure:	Glass fiber (JM100), rock wool, resin-coated glass wool, uncoated glass wool – 10 mg/m^3 for each 7 h/day, 5 days/week for 50 weeks Killed at 4 months postexposure
Results:	Focal fibrosis caused by all fibers; type II cell proliferations; cellular debris and lipid material accumulation; hyperplasia of alveolar cells and cells lining terminal airways

Authors:	**Lee *et al.*, 1981**
Animals:	Charles River CD Sprague-Dawley rats, male (46/group); albino guinea pigs, male (30-35/group); hamsters (34/group)
Exposure:	Fiberglass – 0.7 x 10^6 f/L (length >5 µm) 6 h/day, 5 days/week for 90 days Killed at 20, 50, and 90 days during exposure period and 6, 12, 18, and 24 months postexposure
Results:	At 18 and 24 months postexposure, bronchoalveolar adenomas were present in 2 of 19 rats exposed to fiberglass compared to none in controls, and 2 of 7 guinea pigs compared to none in controls. Alveolar proteinosis was present but was resolved by 2 years postexposure.

Authors:	Pickrell *et al.*, 1983
Animals:	Specific pathogen free (SPF) Fischer rats (32/group)
Exposure:	Glass microfiber – 50,000 f/cc (2500-5000 f/cc >20 µm), count median diameter (CMD) about 0.1 µm, CML about 8 µm, 30-50 mg/m^3, about 70% respirable 5-6 h/day, 2 or 5 days Killed at 1, 4, 5, 8, and 12 months postexposure
Results:	No gross or microscopic findings of significance.

Authors: **Goldstein *et al.*, 1983; Goldstein *et al.*, 1984**
Animals: Baboons (*Papio ursinus*), male (10 animals used but exposure-control distribution not specified).
Exposure: Glass fiber, blend of C102 and C104 – 7.54 mg/m^3 total, 5.80 mg/m^3 respirable, 1122 f/cc >5 µm
7 h/day, 5 days/week, up to 35 months
Lung biopsy at 8, 18, and 30 months during exposure, and 6, 8, and 12 months after exposure.
Results: Early signs of fibrosis after 8 months exposure; fibrosis slightly more marked at 18 and 30 months postexposure. No evidence of tumors.

Authors: **McConnell *et al.*, 1984**
Animals: Specific pathogen free (SPF) Fischer rats (numbers per group not reported)
Exposure: Glass microfiber (JM100) – 10 mg/m^3; UICC Canadian chrysotile B – 10 mg/m^3
7 h/day, 5 days/week for 12 months
Killed at 3, 12, and 24 months
Results: At three months, a minimal to mild cellular change at the junction of terminal airways and proximal alveoli in chrysotile- and glass-exposed animals was observed, but fibrosis was not apparent. At 12 months, chrysotile produced minimal pulmonary fibrosis but glass fiber did not. At 24 months, there was notably less fibrosis observed in animals exposed to glass fiber than those exposed to chrysotile. Compared to controls, increased numbers of neoplasms were observed in animals exposed to chrysotile but not the glass fiber-exposed rats.

Authors: **Smith *et al.*, 1984**
Animals: Osborne–Mendel (OM) rats, female; Syrian hamsters, male
Numbers per group not specified for either species.
Exposure: Glass fiber – 3000 f/cc (about 3 mg/m^3) or 300 f/cc (about 0.3 mg/m^3), 0.45 µm mean diameter
6 h/day, 5 days/week for 24 months, lifetime observation.
Results: No fibrosis or tumors were observed in exposed animals of either species. Observed fibrosis and bronchoalveolar hyperplasia were consistent with controls.

Authors: **Wagner *et al.*, 1984**
Animals: SPF Fischer rats (56/group)
Exposure: Rock wool (without resin coating) – 227 f/cc, diameter <3 µm, length >5 µm; glass wool (without resin) – 323 f/cc, diameter <3 µm, length >5 µm; glass wool (with resin) – 240 f/cc, diameter <3 µm, length >5 µm; Glass microfiber – 1436 f/cc, diameter <3 µm, length >5 µm; UICC Canadian chrysotile – 3832 f/cc, diameter <3 µm, length >5 µm.
All concentrations 10 mg/m^3.
Killed at 3, 12, and 24 months
Results: Some reaction was observed to all fibers but only chrysotile reached a level of "evidence of interstitial fibrosis." Rock-wool exposure resulted in one case of bronchoalveolar hyperplasia (BAH), a benign adenoma, and an adenoma with some characteristics of malignancy. Glass wool with resin resulted in one case of BAH and one adenoma. Glass wool with resin and glass microfiber groups resulted in three cases of BAH and one adenocarcinoma in each.

Authors: **Mitchell *et al.*, 1986**
Animals: 50 male and 50 female Fischer-344 rats and 15 male cynomolgus monkeys were placed into each of five exposure groups

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Exposure: Group 1: 4-6 µm glass fiber, >20 µm in length with red binder, 15 mg/m³ target concentration
Group 2: 0.5-3.5 µm glass fiber, >10 µm long with yellow binder, 15 mg/m³ target concentration
Group 3: <3.5 µm glass fiber, >10 µm in length, 5 mg/m³ target concentration
Group 4: <3.5 µm glass fiber, >10 µm in length, 5 mg/m³ target concentration
Group 5: control, 7 h/day, 5 days/week for 72 weeks (monkeys) and 86 weeks (rats), excluding holidays

Results: Macrophage aggregates with phagocytized fibrous glass in lungs and tracheobronchial lymph nodes of monkeys. Macrophage aggregates and granulomas containing glass fibers were observed in exposed rats. No evidence of fibrogenic response was observed in monkeys or rats. Rats in group 4 showed most severe lesions while group 1 had minimal response. Monkeys exhibited similiar severity in all exposed groups, except group 1, which had minimal response. Neither pulmonary nor mesothelial carcogenicity were found. However, mononuclear cell leukemia (MCL) of the spleen was observed in all rat groups. Two explanations were offered: 1) Fibrous glass in pulmonary or lymphoid tissues may alter the cellular immune function causing an increase in spontaneously occurring MCL. 2) Fibrous glass may have a direct genotoxic effect on stem leukocytes in pulmonary or lymphoid tissues, also increasing MCL.

Intratracheal Instillation

Authors: **Feron *et al.*, 1985**
Animals: Syrian Golden hamsters (35 males and 35 females/group)
Treatment: Glass microfibers (JM104) milled from glass wool, 95% <20 µm, 89% <12 µm, 58% <5 µm, 25% <2 µm length, 88% <1.0 µm, 60% <0.5 µm, 31% <0.25 µm diameter; UICC crocidolite, 90% <20 µm, 78% <12 µm, 42% <5 µm, 21% <2 µm length, 91% <1.0 µm, 67% <0.5 µm, 37% <0.25 µm diameter; 1 mg of fiber in 0.2 ml 0.005% gelatin solution in saline given every 2 weeks for 52 weeks.
Killed at 85 weeks.
Results: No tumors were observed in either glass fiber- or crocidolite-exposed animals. "Silicotic granulomas" were found in glass fiber-exposed animals. These are tightly packed, iron-positive macrophages filled with glass fibers and encased with a layer of alveolar epithelium.

Authors: **Mohr *et al.*, 1984**
Animals: Syrian Golden hamsters – males (135-142/group examined)
Treatment: Glass fibers I (JM104), 50% <7.0 µm length, 50% <0.3 µm diameter; glass fibers II (JM104), 50% <4.2 µm length, 50% <0.3 µm diameter ; UICC crocidolite – 50% <2.1 µm length, 50% <0.2 µm diameter; Titanium dioxide, granular, 1 mg dust in 0.15 ml saline, once per week for 8 weeks.
Survivors kept as long as 130 weeks.
Results: Glass fiber group I exhibited 5 lung carcinomas, 37 mesotheliomas, and 6 thoracic sarcomas. Glass fiber group II exhibited 6 lung carcinomas, 26 mesotheliomas, and 6 thoracic sarcomas. Crocidolite group exhibited 9 lung carcinomas, 8 mesotheliomas, and 1 thoracic sarcoma. Titanium dioxide group had only 2 thoracic sarcomas.

Authors: **Pickrell *et al.*, 1983**
Animals: Syrian hamsters, males, 10-12 weeks old (20/group)
Treatment: Household insulation (Johns Manville) A – 2.3 µm CMD, 21 mg total; household insulation (Certainteed) B – 3.0 µm CMD, 18 mg total; household insulation (Owens-Corning) C – 4.1 µm CMD, 17 mg total; glass microfiber #1 (JM100) – 0.1 µm CMD, 7 mg

total; glass microfiber #2 (JM100) – 0.2 µm CMD, 2 mg total. UICC crocidolite – 0.25 µm CMD, 6 mg total.

Results: All animals receiving glass microfiber #1 were dead within 30 days of instillation. Lungs were hemorrhagic and edematous. Three unscheduled deaths occured in the glass microfiber #2 group. At 1 and 3.5 months, hamsters from the glass microfiber #2 and crocidolite groups showed aggregates of macrophages. At 11 months, these groups showed BAH, chronic inflammation associated with terminal bronchioles and alveolar ducts, and slight pulmonary fibrosis at sites of severe lesions. Larger airways demonstrated goblet cell hyperplasia (GSH). Hamsters from the three household insulation fiber groups demonstrated only focal GSH, BAH, and inflammation appeared as large foamy alveolar macrophages. Mild septal fibrosis was noted in animals from the type A insulation group.

Authors: **Renne *et al.*, 1985**
Animals: Syrian Golden hamsters (25/group)
Treatment: Quartz (0.03, 0.33, 3.3, 6.0 mg); quartz and ferric oxide (0.03, 0.33, 3.3, 6.0 mg each); fibrous glass (0.05, 0.5, 1.0, 10.0mg); hydrated alumina (0.2, 2.0, 5.0, 20.0 mg)
Particle diameters were

	Median	Average	Mass Median	Mass Aerodyn
Quartz	0.84 µm	1.06 µm	3.14 µm	5.13 µm
Ferric oxide	0.27 µm	0.29 µm	0.60 µm	1.37 µm
Alumina	0.50 µm	0.81 µm	6.31 µm	9.81 µm

Fibrous glass had a median diameter of 1.88 µm and a median length of 2.97 µm. 40% of the sample exhibited a length to diameter ratio >3:1 and a median diameter of 0.75 µm and median length of 4.30 µm. 15% of these had lengths >10 µm. 15 weekly instillations were given in each treatment. Each group was killed when survival reached 20%. Remaining groups were killed at about 22 months after first instillations.

Results: Survival was significantly decreased in the groups receiving 3.3 and 6.0 mg of quartz or quartz and ferric oxide, and 0.2 and 2.0 mg of hydrated alumina. Incidence and severity of septal fibrosis correlated well with amount of quartz or quartz and ferric oxide. The correlation with amount of fiber was not as clear in the alumina and fibrous glass groups. The highest incidence of fibrosis occurred in the 10.0 – mg fibrous glass group, but the response was not as great as that observed in the quartz or quartz and ferric oxide groups. There was also a slightly higher incidence of fibrosis in saline controls over untreated controls.

Authors: **Wright and Kuschner, 1977**
Animals: Guinea pigs (30/group)
Treatment: Crocidolite long – >80% >10 µm
Crocidolite short – >90% <5 µm
70% 0.10 µm to 0.30 µm diameter
Total dose: long – 4 mg, short – 25 mg
Synthetic fluoramphibole long – 16% >10 µm, 43% >5 µm
Synthetic fluoramphibole short – >99% <5 µm
Diameters mostly <1.0 µm; 3.5% of long fibers were 1 µm to 2 µm in diameter
Total dose: 12 mg each
Glass fiber long – 92% >10 µm
Glass fiber short – 93% <10 µm
0.10–1.0 µm diameter
Total dose: long – 12 mg, short – 25 mg
Thin glass fiber long – 50% >10 µm
Thin glass fiber short - 100% <5 µm

Mean diameter $<0.10\ \mu m$
Total dose: long - 12mg, short - 25 mg

Killed at 2 years after last injection, only results presented.

Results:
- *Crocidolite*
  Long – Extensive fibrosis was observed, particularly in regions where the lung abutted terminal bronchioles and involved respiratory bronchioles with proximal alveoli. Macrophages in hilar nodes contained short fibers.
  Short – No fibrosis. Many more macrophages with ingested fibers were observed in lymph nodes.
- *Synthetic Fluoramphibole*
  Long – Striking interstitial fibrosis and small groups of macrophages were observed in lymph nodes with "assumed sieved" smaller fibers.
  Short – No fibrosis, but a large aggregate of macrophages was observed in lymph nodes.
- *Glass Fiber*
  Long – Fibrotic lesions, in the areas around terminal bronchioles, were observed in asbestos- exposed animals. The quantitative effect was less than that observed for asbestos exposed animals. Lymph nodes contained large numbers of small fibers.
  Short – No effect was observed other than macrophage aggregation in alveoli. Many fiber-filled macrophages were observed in lymph nodes.
- *Thin Glass Fiber*
  Long – Minimal fibrosis was observed in the area abutting terminal bronchioles. Sheets of macrophages were observed in the lymph nodes.
  Short – No fibrosis but an increased number of macrophages were observed in lymph nodes.

Intrapleural and Intraperitoneal Injection

Authors: **Wagner *et al.*, 1984**
Animals: SPF Sprague-Dawley Rats (48/group)
Treatment:

	Fibers $>5\ \mu m$	Particles $>1\ \mu m$
Swedish rock wool with resin	1.6×10^8	29.4×10^8
Swedish rock wool without resin	2.6×10^8	47.0×10^8
German slag wool with resin	1.2×10^8	25.2×10^8
German slag wool without resin	1.3×10^8	55.0×10^8
English glass wool with resin	2.2×10^8	15.2×10^8
English glass wool without resin	4.2×10^8	19.6×10^8
Glass microfiber (JM100)	30.2×10^8	25.2×10^8
UICC African chrysotile	196×10^8	8.8×10^8

70 mg dust dispersed in 0.5 mL physiological saline was injected intrapleurally; controls received saline only.

Results: Mesotheliomas were found in six rats from the chrysotile group, four from the glass microfiber, three from the rock wool with resin, two from the rock wool without resin, and one from the glass wool (group not indicated). None were observed from the slag wool group.

Authors: **Pott *et al.*, 1984**
Animals: Wistar rats, female (37-44/group); Sprague-Dawley rats, female (45-63/group)
Treatment: Various sample and size-distributions of glass microfiber (JM100 and JM104), rock wool, basalt wool, and slag wool as 2, 5, or 10 mg intraperitoneal injections, or three 25-mg injections.

Further experiments were done with JM104 glass microfiber pretreated with HCl or NaOH 5 mg intraperitoneal injections were administered.

Results: Tumors (sarcomas or mesotheliomas) ranged from 1 in the rock wool group to 73 in a glass fiber (JM104) group. No tumors were observed in the basalt wool group. Carcinogenicity of NaOH-treated JM104 was reduced and carcinogenicity of HCl-treated was greatly reduced when compared to the untreated JM104 group.

Results from animal studies are equivocal. Current scientific discussion weighs epidemiological studies against animal studies. A wide variety of protocols has been used in these studies, further complicating the issues. Therefore, people often cite studies that support their viewpoint and disregard those that do not.

SECTION 5

DURABILITY OF FIBERS IN TISSUE FLUIDS

Morgan and Holmes (1986) and Davis (1986) have reviewed the literature on fiber solubility. They conclude that durability probably plays an important role in determining subsequent toxic effects after exposure to fibers. Chrysotile fibers are less durable than those of crocidolite. It is suggested that, in humans, the effects of crocidolite are more marked than those of chrysotile because the denaturation of chrysotile fibers requires only a few years compared to the life span of man, whereas rodents are more susceptible to the effect of chrysotile fibers since their life will end before the chrysotile fibers have denatured completely (Spurny *et al.*, 1983).

Spurny *et al.* (1983) reported on the chemical and physical analyses of fibers recovered from human and other animal tissues as well as fibers subjected to various leaching solutions. Fibers investigated were UICC chrysotile and crocidolite, glass fibers (JM100, JM104, and JM106) and miscellaneous mineral wool samples (rock wool, slag wool, and basalt wool). Methods of analysis included scanning electron microscopy, microprobe analysis, X-ray diffraction, X-ray fluorescence spectroscopy, and laser microprobe mass analysis. Leaching solutions or environments were 2N HCl, 2N H_2SO_4, 2N NaOH, H_2O, blood serum, animal tissues (rabbit and rat), and distilled H_2O.

Tissues and acidic solutions produced notable chemical changes and structural instability in chrysotile fibers. Magnesium ions were leached out relatively quickly. Silicon and iron were also leached out to some degree. The leaching of magnesium, iron, and silicon varied among the different fibers examined. Leaching was faster for thin fibers than for those with diameters greater than 1.5 µm. Thicker fibers showed varying degrees of leaching along their lengths. Crocidolite was more resistant to these treatments than chrysotile. The MMMF underwent chemical and physical changes similar to chrysotile. In general, MMMF are more resistant to acids and biological tissues

than chrysotile, but less resistant than crocidolite. The glass fibers tended to be more resistant than the other MMMF examined.

Forster (1984), Klingholz and Steinkopf (1984), and Leineweber (1984) studied the effects of MMMF in water and artificial physiological solutions. In general, most MMMF were softened in physiological solutions expressed as gel formation on the fiber surface. Removing this gel exposed the remaining fiber core for the next attack by the solution.

Morgan and Holmes (1984) reported on the marked solubility of fibers following intratracheal injection of glass fibers of known size. Longer fibers, 60 µm in length, solubilized more quickly than fibers of 5 and 10 µm in length. The difference in rate was attributed to the difference in pH between the external environment encountered by the long fibers and the intracellular environment of the macrophages that engulfed the shorter fibers. Long rock wool fibers seemed more durable than glass fibers. Similar differences in long fiber-short fiber dissolution rates were found by Bernstein *et al.* (1984).

SECTION 6

CERAMIC FIBERS

Gross *et al.* (1956) studied the effects of intratracheal injection of a synthetic ceramic fibrous material (Fiberfrax, Carborundum Corp., Niagara Falls, NY) on the lungs of young male rats (unspecified strain). The material used was a white cotton-like mass of fibers, ranging from 0.1 µm to 10 µm in diameter, and 2.5 µm to 25 mm in length. Chemically, it contained about equal portions of alumina and silica, with less than 2% minor additives (boric oxide or zirconia).

Fiber dusts were produced in two different sizes for administering to the animals. These sizes were described as "coarse" and "fine" dusts. The coarse dust varied widely in fiber dimension and shape. The fine dust had a mean particle size of 0.04 µm ± 2.0 (SD). 50 mg of coarse ceramic dust and varying amounts (3.3-72.0 mg) of fine ceramic dust were administered. 13 spontaneous deaths, generally caused by pneumonias, occurred in the group of 19 rats receiving the coarse dust. Immediate deaths occurred in 4/4 receiving 72.0 mg; 1/1 receiving 37.7 mg; 2/2 receiving 13.4 mg; and 1/1 receiving 6.7 mg in a single injection of fine dust. Delayed death (24 to 48h) occurred in 2/2 receiving 3.3 mg in a single injection and 1/1 receiving 6.6 mg in 2 injections of fine dust. Deaths occurred months later in 1/1 receiving 9.9 mg in 3 injections and 3/13 receiving 13.2 mg in four injections. Control dusts were quartz, feldspar, and limestone. Similar patterns of spontaneous deaths resulted from injecting both coarse and fine dusts of quartz and feldspar. However, one

death occured out of 12 animals injected with 75 mg of coarse limestone dust, and months later, 8 deaths occured out of 12 animals injected with 70.7 mg of dust. The investigators attached no significance to the differences in mortality rates among the various experimental groups.

Survivors among the animals treated with coarse dust were killed at 12 months. Local tissue reaction was observed around and near respiratory bronchioles where larger dust particles tended to lodge. Well-delineated, thin, fibrous tissue capsules surrounded the fibers. In addition, there were "scattered, smaller and less obvious foci of relatively acellular and bland fibrous thickening" of alveolar walls. In about one-quarter of the animals, these foci were associated with obviously distorted alveoli having incomplete expansion of some air spaces and overexpansion of others. Moderate collagenous thickening of interlobular septa was noted in a few animals. The cellularity of the fibrous tissue was not excessive. All rats that died after six months posttreatment with the fine dust showed a minimal focal collagenous thickening of alveolar walls. Several rats had occasional larger areas of fibrosis. Dark brown to black pigment granules were observed in alveolar macrophages from animals exposed to either coarse dust or fine dust. The authors claim that these granules were probably a contaminant of the fiber dust, a component of the material as received.

From their findings the authors concluded that the ceramic fiber dusts were essentially inert and the observed pathological symptoms were "nonspecific." However, a good description of fiber sizes and size distributions was not provided; sample sizes of the experimental groups were small; and there were some difficulties in administering the fibers.

Wagner *et al.* (1973) reported on a series of four experiments in which SPF Wistar rats were injected intrapleurally with asbestos and other materials, including a synthetic ceramic (aluminum silicate) fiber, fiberglass (borosilicate), glass powder (borosilicate), and aluminum oxide. The description of preparation and/or size of each material as provided by the authors follows.

- Chrysotile – superfine sample settled out in water to separate from grade 7, the most fully milled commercial product.
- Ceramic fiber – Prepared by grinding in a ceramic ball mill and extracting the respirable fraction by settling out in air. Fiber diameters ranged between 0.5 and 1 µm.
- Fiberglass – Nominal diameters of fibers between 1.5 and 2.5 µm; 30% were actually in this range, with range extending to 7 µm. Sample prepared by embedding fibers in water-soluble wax, chopping in microtome, and washing away wax. More than 60% of fibers were longer than 20 µm.
- Glass powder – All in respirable range (<8 µm projected area diameter).

- Aluminum oxide – Nonfibrous material all in respirable range (<10 μm projected area diameter).

Twenty milligrams of material was administered to each animal within groups of up to 36 animals. (Due to a shortage of animals, less than 36 animals were used in some groups, and animals lost to injection fatalities were not replaced). Materials were suspended in physiological saline at concentrations of 50 mg/mL. For results see Table 1.

TABLE 1. RESULTS OF STUDY BY WAGNER *ET AL.* (1973)

	Number of Rats Studied	Number of Rats With Mesothelioma	Survival Time (days) of First Mesothelioma	Mean Survival of all Rats (Days)	Estimated Carcinogenicity Factor ($\times 10^9$)
Ceramic fiber	31	3	743	736	0.16
Fiberglass	35	0	---	774	---
Glass powder	35	1	516	751	0.04
Aluminum oxide	35	1	646	710	0.05
Chrysotile	36	23	325	568	2.85
Chrysotile (2nd sample)	32	21	382	639	2.28

The carcinogenicity factor (CF) summarizes the esothelioma occurring in each group. The CF reflects the percentage of animals that developed a mesothelioma over time after inoculation. The CF also corrects for mortality from other causes, so that chance variation in mortality between different treatment groups does not affect comparisons. In comparing the results of this experiment with three others (concerned mainly with asbestos), the authors relate their findings to "significant" fiber size (those that are less than 0.5 μm in diameter and greater than 10 μm in length). They argue that fiber size (physical properties) is an important factor associated with mesothelioma development.

Results of experiments of this sort can be criticized because the fibers are not administered by inhalation. However, by placing known quantities of a material at a site where mesotheliomas may develop, useful information is obtained regarding the comparative potency of materials to induce mesotheliomas.

In a letter to the editor, Matalani (1978) proposed the use of Kaowool as a substitute for asbestos. Kaowool is a ceramic fiber made from kaolin. The author stated (without reference) that when heated at 1250°C for 500 h, 30 to 45% of a crystalline form of silica (cristobalite) is present in the fused material for extended periods of time. He also said that Kaowool is believed to be inert when inhaled, as long as it has not been exposed for extended periods to temperatures in excess of 1100°C.

Matalani clearly recognized that ceramic fibrous material, when subjected to excess heat over prolonged periods of time, forms crystalline silica. He further advised using dust control measures when such heat-treated Kaowool is being dismantled.

Pigott *et al.* (1981) reported the results of an inhalation study in which the effects of refractory alumina fibers (Saffil, I.C.I.), either in a manufactured or a thermally aged form, were compared to UICC chrysotile A asbestos and clean air, as positive and negative controls, respectively. The Saffil alumina fiber consists of aluminum oxide with about 4% silica. Albino rats of the Alderley Park (Wistar-derived) strain were exposed for 86 weeks to the Saffil fibers or for 77 weeks to asbestos. Animals were maintained until an 85% average mortality of all groups was reached; remaining animals were killed at that time. In addition, interim killings were carried out at 14 weeks and 27 weeks (2 of each sex per group) and 53 weeks (1 of each sex per group). The Saffil fibers had a median diameter of about 3 µm and a median length ranging from 35 to 62 µm. These fibers were ball-milled prior to use for the last eight weeks of exposure. The ball-milling process did not affect fiber diameter, but the median length was reduced to about 10 µm. The thermally aged Saffil was heated to 1200 or 1300°C for 100 h, or 1300°C for 1000 h. Median diameters of these fibers were also about 3 µm, and median lengths about 55 µm. Sizes of the asbestos fibers were not given. Relatively low concentrations of respirable dust were generated, 2.18 and 2.45 mg/m^3 for Saffil and thermally-aged Saffil, respectively. Asbestos was kept at a mean concentration of 4.57 mg/m^3. As expected, progressive asbestosis was observed in the chrysotile-exposed animals. Benign and malignant pulmonary neoplasms were observed only in chrysotile-exposed animals. Of the nonrespiratory tract tumors, there was no significant difference between groups as the tumor types were primarily those commonly observed in this rat strain. Reported results for Saffil fibers are consistent with their nuisance dust classification.

Leineweber (1984), recognizing that fiber durability is a determinant of the extent of biological activity, reported on an *in vitro* study of fiber dissolution in saline and water. Of the fibers tested four were glass, one mineral wool, and one refractory fiber. In these solubility experiments, a continuous flow system minimized the effect of dissolved components on the dissolution rate. The physiological saline was buffered and remained at essentially neutral pH throughout the extractions. The water extractions had effluent pH as high as 8 or 9 for those samples that were readily attacked. The results were expressed as a rate constant with units of gram per square centimeter of surface per hour. This rate constant can be used as an index of fiber solubility or durability in a test solution. There was a 30-fold range of fiber durability in water and 40-fold range in physiological saline. The refractory fiber was the most durable in water and the second most durable in saline. Attempts to correlate solubility rates with chemical composition were not conclusive.

Hammad (1984) noted that glass fibers, when inhaled, reportedly behave like inert dust, but when administered intratracheally, intraperitoneally, or intrapleurally, may induce fibrosis, lung tumors, or mesotheliomas depending on the injection site and physical dimensions of the fibers. His study showed that differences in the results of inhalation and implantation studies are related to the durability of fibers and their ability to clear from the lungs of rats (unspecified strain). Two groups of 49, three-month-old male rats were exposed by inhalation to an aerosol of mineral wool fiber for 6 h per day for 6 consecutive days or to ceramic fiber for 6 h per day for 5 consecutive days.

TABLE 2. CHARACTERISTICS OF FIBERS

	Mean Fiber Concentration (f/cc)	Standard Deviation	Count Median Length (μm)	Geometric Standard Deviation	Count Median Diameter (μm)	Geometric Standard Deviation
Mineral wool	300	82	13	2.6	1.2	1.8
Ceramic fiber	303	17	9	3.1	0.7	2.3

Animals were killed at 5, 30, 90, 180, and 270 days. Fibers were recovered from the lungs by ashing and washing. The half-lives needed to clear from the lung differed between ceramic and mineral wool fibers. At 270 days, approximately 25% of the ceramic fibers were still present in the lung compared with 6% of the mineral wool fibers. Diameter and length distributions were similar for both fibers. Notably, the results are consistent with the ceramic fibers, being more resistant to chemical attack than the glass wool fibers. It remains to be shown whether solubility alone determines the extent inhaled fibers clear from the lung.

Davis *et al.* (1984) reported on the effects of ceramic aluminum silicate fibers administered intraperitoneally and by inhalation to SPF Wistar rats of the AF/HAN strain. Forty-eight 3-month-old rats were exposed to ceramic fiber dust 7 h per day, 5 days per week for 224 days during a 12-month period. Forty control animals were maintained over the same time period. Animals were killed at 12, 18, and 32 months from the start of the exposure. The mean fiber mass concentration during exposure was 10.0 mg/m^3 ± 4.8 mg/m^3 (SD). Counts of fibers using phase-contrast microscopy gave a concentration of 95 f/cc for fibers longer than 5 μm, narrower than 3 μm, and aspect ratio greater than 3:1. Long and thin fibers were very rare. Using scanning electron microscopy, the authors determined that about 90% of fibers were less than 3 μm long and 0.3 μm wide. These fibers made up the bulk of the dust cloud by numbers. Survival for both the treated and control animals were similar. Unlike results from rats exposed to chrysotile in the same laboratory, peribronchiolar fibrosis was virtually nonexistent in the ceramic-fiber-treated animals. However, interstitial fibrosis, which also occurs as a result of chrysotile exposure, was present to a lesser extent, but was stated to be not significantly different (p-value not indicated) than that observed after chrysotile exposures. Eight animals exhibited pulmonary neoplasms resulting from exposure to the ceramic fibers; no control

animals were so affected. Of the observed neoplasms, one was a benign adenoma, three were carcinomas, and four were malignant histiocytomas. The overall pattern was different, however, than that observed for asbestos exposure. Similar numbers of nonpulmonary tumors were found in exposed and control groups. The intraperitoneal injections of ceramic fiber dust caused three animals to develop peritoneal tumors. Thus, 9.3% of the animals responded compared with 90% previously affected after similar exposure to asbestos preparations. An interesting difference in the ability of these fibers to induce tumors was noted: The first tumor did not appear until about 850 days after injection with ceramic dust, yet tumors appeared as soon as 200 days after injection with chrysotile.

Gantner (1986) reported exposure hazards that result when various brands of ceramic fiber insulation were removed from industrial furnaces. When ceramic fibers consisting of alumina-silicate are exposed to high temperatures over extended periods of time, the fibers devitrify and transform to cristobalite, a crystalline form of free silica. If workers are exposed to elevated levels of crystobalite over long periods of time silicosis can develop (Rice *et al.*, 1984; U.S. Department of Health, Education, and Welfare, 1977). Short-term exposures at very high levels can cause acute silicosis, or death from exposure within three years (Ziskind *et al.*, 1976). As part of a larger study on the energy efficiency of ceramic fiber insulation in industrial furnaces, an industrial hygiene study was performed while several brands and forms of ceramic fiber insulation were being removed from furnaces. Three brands of insulation, in either blanket or brick module form, were subjected to maximum furnace temperatures of 2000°F (1094°C) to 2550°F (1399°C) for 100 to 471 h. After removal, these bulk samples of insulating material were found to contain 3 to 21% cristobalite. Air samples taken at the same time contained from 4.0 to 14.7% cristobalite. Respirable and total dust samples were collected simultaneously using personal and area samplers.

TABLE 3. CHARACTERISTICS OF RESPIRABLE AND TOTAL DUST SAMPLES

	Personal Samplers			Area Samplers		
	Mean	Range	SD	Mean	Range	SD
Respirable dust	4.99	0.12-16	6.68	1.61	0.1-3.4	1.59
Total dust	3.95	0.31-35	16.8	8.98	0.96-36	2.42

All values are in mg/m^3

Since the study was designed for energy research, the variables of time and temperature were not adequately monitored to relate them to cristobalite formation. However, cristobalite formed in all three brands of insulation under all exposure regimes examined.

Smith *et al.* (1986) reported an extensive study of long-term health effects in hamsters and rats that were chronically exposed intraperitoneally, intratracheally, or by inhalation to several MMMF. Fibers studied through inhalation exposure included four glass fiber configurations, a mineral wool, and a refractory ceramic fiber. UICC crocidolite asbestos and clean air served as positive and negative controls, respectively. One-hundred-day-old, male Syrian hamsters and female OM rats received nose-only exposures for 6 h per day, 5 days per week, for 24 months. Animals were maintained for their lifetimes. In similar groups, hamsters and rats received an intraperitoneal (IP) injection of 25 mg of fiber suspended in 0.5 mL physiological saline. The fibers used were glass, refractory ceramic, and crocidolite. These fibers were obtained from airborne samples collected from the respective inhalation exposure chambers. The same three types of fibers were instilled intratracheally (IT) to additional groups of animals. Instillation occurred once a week for 5 weeks using 2 mg of fiber suspended in 0.2 mL of physiological saline, so that a total of 10 mg was administered. Animals from the IP and IT experiments were also maintained for their lifetimes.

Many inconsistent differences were observed in the life spans of animals exposed by inhalation to MMMF when compared with unmanipulated cage control groups. However, of the hamsters receiving refractory ceramic fibers IP, 21 out of 36 died from acute hemorrhagic peritonitis and vascular collapse within 30 days. A second group was then similarly injected, and 15 of 36 died within 30 days. Those from both groups surviving 30 days were stated as having had significantly (probability not stated) shorter life spans than the controls. The OM rats apparently did not develop hemorrhagic peritonitis, although they had significantly reduced mean life spans because of abdominal mesothelioma induction. The only animals having shorter life spans than the controls were hamsters administered refractory ceramic fiber. However, none of these hamsters developed primary lung tumors, and there was no increase in the level of pulmonary fibrosis.

All lung lesion levels were below the grade that would indicate the occurrence of collagen deposition. The lack of a fibrous component may mean that the observed lesions are potentially reversible. Pulmonary lesions did not progress after stopping the 24-month exposure to MMMF. The only remarkable finding was that one of the 70 hamsters from the ceramic fiber inhalation group died after 10 months of exposure and had a 2 cm diameter spindle cell mesothelioma in the ventral, posterior area of the left lung. The presence of the single tumor in one hamster was not statistically significant, but because of the association between fibers and mesothelioma induction, it must at least be considered. Spontaneous mesotheliomas are considered rare, but one was reported in an adult male hamster (Fortner, 1961); however, its precise location was not noted. No other primary lung tumors were detected in the animals exposed to MMMF. A large peripheral benign mucous-secreting bronchoalveolar tumor was observed in a chamber control hamster from this same study.

Of the retained fibers that were recovered from the lungs, the glass and mineral wool fibers were highly etched , whereas the ceramic fibers showed no sign of etching.

Abdominal mesotheliomas were observed in all animals receiving IP doses of fibers; none were observed in the controls. None of the animals receiving IT instillations of MMMF developed primary lung tumors.

SECTION 7

DISCUSSION

To date, the epidemiological evidence indicates that non-ceramic MMMF is relatively safe particularly when compared to asbestos. However, most reviews and reports still add a conservative note stressing the need for further research. Sir Richard Doll's summary statement at the recent WHO/IARC conference ended with a conservative statement even though the newest epidemiological information indicated a low risk of cancer among production workers in the nonceramic MMMF industry (Doll, 1986).

The animal studies with nonceramic MMMF showed a variety of findings. There were no remarkable findings in some of the inhalation studies of rats and hamsters exposed to glass fibers, intratracheal studies of hamsters treated with glass fibers, or intrapleural studies of rats treated with glass fibers. Fibrotic responses resulted from inhalation exposures of rats to glass fibers, and rock or glass wool; of baboons to glass fibers; and after intracheal instillation of hamsters and guinea pigs with glass fibers. Carcinomas resulted from inhalation exposure of rats to glass fibers or glass wool and from intratracheal instillation of hamsters with glass fibers. Adenomas resulted from inhalation exposure of rats to glass fibers, and rock or glass wool, and of guinea pigs to glass fibers. Mononuclear cell leukemia of the spleen resulted from inhalation exposure of rats to fibrous glass. Sarcomas resulted from intratracheal instillation of hamsters with glass fibers and from intraperitoneal injection of rats with glass fibers. Mesotheliomas resulted from intratracheal instillation of hamsters with glass fibers, intrapleural injection of rats with glass fiber, rock or glass wool, and intraperitoneal injection of rats with glass fibers.

The experimental evidence for nonceramic MMMF, as outlined in this report, presents a complex and incomplete picture. Inhalation exposures are the most relevant since this is the means by which man is most often exposed. The results of such studies range from minor tissue reaction with small accumulations of macrophages, to some signs of fibrosis, to the presence of bronchoalveolar adenomas. Intratracheal instillation also produces a range of results with the most

severe being lung carcinomas, mesotheliomas, and thoracic sarcomas. Intrapleural and intraperitoneal studies produce a range of sarcomas and mesotheliomas. Interpretating this range of results leads to several key points. Inhalation studies, which should produce the most relevant information for assessing human risk, are probably the most difficult to interpret. Basically, there are too many variables in the studies conducted to date. These variables include species, age and sex of animals, type of material studied, size of fibers, ratio of fibrous to nonfibrous dust, method of generation, concentration of dust, duration of exposure, duration of study, time points of kill, and methods of analysis. Deposition, retention, and translocation patterns in the animals are additional variables in inhalation studies. Intrapleural and intraperitoneal studies are, perhaps, easiest to perform in a uniform manner but represent an artificial means of exposure. They are still useful for ranking the tumorigenic potential of different materials. Locally injected doses may be higher than inhaled doses, leading to hemorrhagic lesions and early death; however, when localized, the injected material can be measured more accurately. The effectiveness of intratracheal instillation lies somewhere between inhalation and intrapleural/ intraperitoneal injection when considering the above-mentioned problems and benefits.

Another issue that must be considered is the durability of fibers, which are eventually dissolved by tissue fluids. Fiber size and shape, chemical surroundings, and time seem to interact and determine the fate of the fiber. Of course, the result also depends on the type of fiber (or particle). The fiber type (and its chemical composition) should be known since the durability characteristics of a fiber are affected by the variables mentioned above. Fiber shape and size must be described (this is complicated since many dusts have a range of shapes and sizes), and site of deposition must be determined (so that its chemical surroundings can be described).

Still another factor, one which is rarely considered, is the life span of the animal species used. With rodents, higher doses are typically used (because of the shorter life spans of the animals) in an attempt to define what happens to man with a lower dose over a longer lifetime. Clearly, this causes a problem with the fiber studies. The dissolution characteristics of different fibers in a particular biological environment are likely to remain constant from species to species. Therefore, a fiber reaching a particular state of dissolution over the life span of a rat may have a much different effect on the rat than it would on man over the same short time period when compared to his total life span. It appears that the studies conducted on baboons (Goldstein *et al.*, 1983; Goldstein *et al.*, 1984) may have been done over too short a period of time. Progressive fibrosis was observed in these studies, but the studies were not carried through to see if tumors developed. We need more information on the fate of fibers, tracking them from initial deposition at a site to final dissolution before assessing an appropriate animal for use in such studies. The life spans of laboratory rodents appear to be too short.

No epidemiological studies and only a few animal studies have been published about ceramic fibers. The two most important studies to consider, because of their positive findings, are those by Davis *et al.* (1984) and Smith *et al.* (1986). The evaluations and conclusions drawn from these studies are difficult to interpret because the findings are positive, and they show discrepancies. Davis reported progressive pulmonary fibrosis and a high incidence of unusual pulmonary tumors in rats exposed by inhalation, and a minimal tumor response in rats injected intraperitoneally. Smith reported no fibrosis and no tumors in rats exposed by inhalation, and a high incidence of tumors in rats injected intraperitoneally. Lethal acute hemorrhagic peritonitis occurred in most of the intraperitoneally injected hamsters but not in the rats of the Smith study. There was a single, very rare pleural mesothelioma reported in a hamster from the Smith study. Due to the findings from these studies and the lack of additional information, the MMMF industry has been forced to support further studies on ceramic fibers (Babcock & Wilcox, 1985; Sohio Carborundum, 1985). These additional studies have yet to be conducted.

The studies of Leineweber (1984) and Hammad (1984) show that ceramic fibers are more durable than other MMMF. Thus, if appropriately shaped fibers are deposited that cause fibrosis and/or tumorigenesis, lesions may be produced because dissolution does not take place, because dissolution does take place, or because of the sheer mechanical load of the fibers.

Additionally, due to their high-temperature insulative properties these ceramic fibers will most likely be used in furnaces and boilers. When subjected to high temperatures they form cristobalite (Gantner, 1986), currently known for its negative health effects.

SECTION 8

AREAS OF NEEDED RESEARCH

Since long-term assays aimed at assessing the carcinogenicity of various fibrous materials were first undertaken, the technology for characterizing airborne particles has advanced and the design of bioassays has been refined. These advances should be used in future studies to make the data from investigations more comparable. This would provide comparability among fibrous materials and comparison to nonfibrous agents.

Toxic and carcinogenic potential among fibers may be compared using short-term *in vitro* methods. Assays have been developed for assessing the genotoxic potential of particulate agents including fibers. Comprehensive *in vitro* data on a variety of fiber materials would help prioritize expensive and lengthy *in vivo* investigations.

Fiber dose-response relationships should be defined relative to asbestos. These studies should use a uniform protocol in which only the fiber type and dose vary. Such studies would avoid the difficulties that prevent comparison between published studies. After the noncarcinogenic toxic effects of fibers have been established by dose-response studies, a second set of studies should be performed under the same guidelines to evaluate relative carcinogenic potential.

Methods need to be improved for analyzing the fiber size and mass of dusts in the atmosphere, both in a chamber and in the workplace. Although not addressed in this review, better methods are needed for characterizing fibers in the field.

More information is needed on fiber durability at different tissue sites and the role of fiber size and composition in inducing fibrosis and/or tumorigenesis. *In vitro* investigations may give insight into these relationships.

Information is needed on the fibrogenic and tumorigenic potential of the cristobalite-containing insulation removed from ceramic-lined furnaces and boilers. This is an important issue for the Navy because they use ceramic-lined boilers.

SECTION 9

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